Ungar, Susan

To: STIC-ILL
Subject: Papers for examination of SN 09/922718

Hi

I need the following papers for examination of SN 09/927718)

1. Sier et al, Gastroenterology, 1994, 107:1449-1456)

2.Ganesh et al, Cancer Res., 1994, 54:4065-4071).

3. Janicke et al, Sem. Throm. Hemostasis, 1991, 17:303-312)

4. Nekarda et al (Cancer Res., 1994, 54:2900-2907)

5. Grandahl-Hansen et al, 1993, Cancer Research 53:1513-1521)

6. JOURNAL OF NEURO-ONCOLOGY, (1994) Vol. 22, No. 2, pp. 139-151.

7. INTERNATIONAL JOURNAL OF ONCOLOGY, (MAR 1994) Vol. 4, No. 3, pp. 717-721.

8. Biol.Chem.Hoppe Seyler (376, No. 5, 259-67, 1995) 2 Fig. 67 Ref.

I NEED THESE ASAP, IF AT ALL POSSIBLE

Thanks
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CM1-8B05

1. The Election filed May 12, 2003 (Paper No. 6) in response to the Office Action of March 11, 2003 (Paper No. 5) is acknowledged and has been entered. Claims 1-69 are pending in the application and Claims 2-4, 7-11, 13-15, 20-27, 31-69 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1, 5-6, 12, 16, 17, 18, 19, 28-30 as they are drawn to a method for screening for the likely progression of a malignant tumor wherein the tumor is colon cancer wherein the tissue assayed is tumor tissue wherein the assay used is immunoassay are currently being examined.

2. Applicant's election of the invention of the determination of variable 4, the likely progression of a malignant tumor in a subject, with marker (I) PAI-1 protein abundance, from Groups 1-96, Applicant's election of Group 99, colon cancer, Applicant's election of Group 135 drawn to detecting progression of a malignant tumor wherein the malignant tumor is a hematological malignancy, Applicant's election of species A, tumor tissue, species B, immunoassay, specie C antibody secreted by clone 1 with traverse is noted. It is further noted that the election of Group 135 is wholly inconsistent with the rest of the election since it is not drawn to the likely progression of a malignant tumor in a subject with colon cancer, but rather is drawn to a method of prognosis of an individual having a malignant tumor wherein the tumor is a hematological tumor which is a method that is independent and distinct from the methods elected in items (1) and (2) of the response because the methods are materially distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success and because a divergent search is required since searches of the two methods would not be coextensive and it is independent because they are not disclosed as capable of use together and they have different modes of operation, different functions or different effect. In the instant case the two inventions are drawn to the assay of different tumor types with different etiologies, different pathologies, different tissue types and they have different functions because each is

drawn to a different type of tumor. Thus Group 135, drawn to prognosis of an individual having a hematological tumor is withdrawn from consideration. Further, the election of the antibody of clone 1 is moot because Applicant has not elected a combination that includes marker ii to which clone 1 refers (see claim 66)

The traversal is on the ground(s) that (a) Examiner has not done a "burden analysis" or identified the classification of each group as required by MPEP 808.02, (b) has not shown that the inventions are independent or distinct and there is a serious burden on the examiner if restriction is not required, thus the restriction requirement is procedurally defective and should be vacated.

As drawn to item (a) above, the argument has been considered but has not been found persuasive because although Applicant has stated that the reference to Inventions III-VII is not understood, the recitation of Inventions III-VII rather than Inventions 1-142 is clearly an inadvertent typographical error given the recitation above section 3 which is clearly drawn to the 142 different methods of the invention. It is clear that the materially distinct methods discussed were meant to refer to Inventions 1-142, thus the burden drawn to the examination of those Inventions has been disclosed. Further, classification is not required when the office has established burden since in this case a divergent search must be done for each of the claimed inventions. Although the searches would be expected to be overlapping, there is no reason to expect that they would be coextensive. A search for each method requires a particular set of search terms focusing on the elected invention. These search terms would be required to change with each elected invention. The arguments have not been found persuasive and the restriction requirement is maintained.

As drawn to item (b) above, Applicant argues that the claims are combination/subcombination claims and that, as drawn to Groups 1-96, Examiner has not demonstrated two way distinctness. Applicant points specifically to MPEP 806.05(c). Upon review it is found that Applicant is correct however, the argument

that requirement should be vacated is not found persuasive because Applicant's response has clearly demonstrated the issues involved are understood and Applicant has properly elected an invention that will be examined as elected.

Further, the reasons why the inventions are patentably distinct are set forth as follows:

(1) Inventions 1 through 96 are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the patentability of the combination does not rely necessarily and solely on the patentability of any one subcombination and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the patentability of the combination does not rely necessarily and solely on the patentability of any one subcombination as clearly evidenced by the plural subcombinations claimed. Further, each of the subcombinations has utility by itself because each of the subcombinations are useful for screening for different variables and different markers. Thus the claims are distinct as required by MPEP 806.05(c).

(2) Inventions 97-109 are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions or different effect. In the instant case the different invention are drawn to the assay of different tumor types with different etiologies, different pathologies, different tissue types and they all have different functions because each is drawn to a different type of tumor. It is noted that inventions that are independent are by their nature 2-way patentably distinct.

Applicant further argues that there is a very close relationship among the four variables. Variable 1 is determining if the subject has a tumor at all, Variable 2 is determining if the tumor is malignant, variable 3 is determining if the tumor is likely to metastasize, variable 4 is determining the likely progression of a malignant tumor and these variables **may** (emphasis added) be highly correlated and variable 3 **seems** (emphasis added) to be a subset of variable 4. The argument has been

considered but has not been found persuasive because the claims are not drawn as applicant suggests, but rather are drawn to a screening method for better ascertaining at least one variable selected from the group of (1) the likelihood of the presence of a tumor, the likelihood of the presence of a malignant tumor, the likelihood of the presence of a tumor metastasis and the likely progression of a malignant tumor in a subject. Although Applicant hypothesizes that these variables may be highly correlated and that variable 3 seems to be a subset of variable 4, neither the correlation nor the relationship of variables 3 and 4 are known since that correlation clearly depends upon parameters not considered, such as tumor type and tumor stage. The arguments have not been found persuasive and the restriction requirement is maintained. However, the Office will reconsider its decisions if such a correlation or relationship between variables 3 and 4 comes to light in any of art that is uncovered during examination of the elected group.

Applicant further argues that it is not very probable that a restriction among variables 1-4 will satisfy the two-way distinctness test and even if assays for these four variables were considered distinct, it does not follow that assays for the variables as analyzed by factorial analysis would satisfy the two-way distinctness test. The argument has been considered but has not been found persuasive because the claims are not drawn to the four variables alone, but rather to the combination/subcombination limitations of both variables and markers. For the reasons set forth above, two-way distinctness has been demonstrated for the inventions of Groups 1-96 and the restriction requirement is maintained.

Applicant further argues, in regard to criterion (A) of MPEP 806.05(c), the criterion is not satisfied because the combination does require the particulars of the subcombination for patentability. The argument has been considered but has not been found persuasive because the patentability of the combination does not rely necessarily and solely on the patentability of any one subcombination as clearly evidenced by the plural subcombinations claimed. It is noted that the Office will

consider rejoinder of combinations encompassing the elected subcombination should the elected subcombination be determined to be allowable.

Applicant further argues that there is arguably a subcombination/combination relationship between (I) and (iii) and between (ii) and (iv), that is because determining the change necessarily requires determining the abundance on at least two occasions. The argument has been considered, but has not been found persuasive because the claimed inventions are not drawn to the markers alone, but rather to the combination of the markers and the variables and for the reasons set forth above, two way distinctness has been established for the claimed inventions. The arguments have not been found persuasive and the restriction requirement is maintained.

Applicant further states, as drawn to the markers, that he is not prepared to say whether or not criteria (A) and (B) of MPEP 806.05(c) are satisfied and would like to see Examiner's position on this. It appears that Applicant cannot determine whether or not distinctness is lacking. Examiner's position on this is clear. The inventions drawn to the variables and markers satisfy the requirements of criteria (A) and (B) of MPEP 806.05(c).

Applicant further argues that with regard to (i) the PAI protein and (ii) the complex the onus is on the Examiner to show two-way distinctness. The argument has been considered but has not been found persuasive since two-way distinctness of the inventions of the combined variables and markers has been established for the reasons set forth above. The arguments have not been found persuasive and the restriction requirement is maintained.

Applicant argues that, as drawn to Groups 97-109, the restriction on the basis of tumor type are generally species restrictions and Claim 1 is generic to all of these inventions and Applicant should have the opportunity to establish that a generic claim is allowable. The argument has been considered but has not been found persuasive because claim 1 has been determined to be a linking claim and Applicant

has the opportunity to establish that the generic claim is allowable. As clearly stated upon the allowance of the linking claim, the restriction requirement as to the linked inventions shall be withdrawn. The arguments have not been found persuasive and the restriction requirement is maintained.

Applicant specifically asks for an explanation of the difference between Group 111a and the group within 1-96 combining variable (2) and marker (i) as they appear to be drawn to the same inventions. As drawn to Group 111a, Applicant is correct and Group 111a is rejoined to the inventions of Groups 1-96.

Applicant further argues that Groups 110-121 do not seem related to claims 97-109, despite the wording of the restriction. Most of them appear to cover the same inventions as those set forth in Groups 1-96. This argument is confusing as it is not clear how claims that do not seem related to claims 97-109 can cover the same inventions as those set forth in Groups 1-96. Further, inventions claimed in claim 36 and the claims dependent on claim 36 that are drawn to variables and markers recited in claim 1 were joined to the inventions of Groups 1-96. However, for the sake of clarity of the record, the reasons why the inventions of Groups 110-121 are patentably distinct are set forth as follows:

(1) Inventions 110-121 are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the patentability of the combination does not rely necessarily and solely on the patentability of any one subcombination and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the patentability of the combination does not rely necessarily and solely on the patentability of any one subcombination as clearly evidenced by the plural subcombinations claimed. Further, each of the subcombinations has utility by itself because each of the subcombinations are useful for screening for different variables and different markers. Thus the claims are distinct as required by MPEP 806.05(c)

(2) Inventions 122-138 are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions or different effect. In the instant case the different invention are drawn to the assay of different tumor types with different etiologies, different pathologies, different tissue types and they all have different functions because each is drawn to a different type of tumor. It is noted that independent inventions are by their nature two-way patentably distinct.

Applicant argues that there is a plain relationship between the mRNA level and the protein level; absence the showing of an unsuspected difference these are not distinct so that the RNA marker should be joined with the protein marker. The argument has been considered but has not been found persuasive because those of skill in the art understand that there is not a plain relationship between the mRNA level and the protein level. Evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For instance, Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teach that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Eriksson et al (Diabetologia, 1992, vol. 35, pp. 143-147) teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby. Hell et al (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Powell et al (Pharmacogenesis, 1998, Vol. 8, pp. 411-421) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of

said protein is highly complex. Carrere et al (Gut, 1999, vol. 44, pp. 55-551) teach an absence of correlation between protein and mRNA levels for the Reg protein. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. Guo et al (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-translational level. These references serve to demonstrate that levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression and that there is not a plain relationship between the mRNA level and the protein levels. Clearly these two markers are distinct. The arguments have not been found persuasive and the restriction requirement is maintained.

Applicant further argues that Groups 112-121 must be compared with the subcombination groups according to combination /subcombination restriction practice and further, for distinction between detecting "presence" and detecting "progression" applicant refers to the previously comments. The argument has been considered but has not been found persuasive for the reasons set forth above.

Further Applicant argues that groups 122-140 raise issues similar to those already addressed, i.e. location of tumor, presence vs. progression vs prognosis. The arguments have been considered but have not been found persuasive for the reasons set forth previously. The arguments have not been found persuasive and the restriction requirement is maintained.

Applicant argues that groups 141 - 142 have a subcombination/combination relationship and that both Groups 141 and 142 have a subcombination/combination relationship to the clinical claims of groups 1-96. The argument is persuasive and the claims of Groups 141-142, Claims 44-50 are rejoined to the inventions of

Groups 1-96. The arguments have not been found persuasive and the restriction requirement is maintained.

Applicant again states that groups 1-96 are not classified and that although the other inventions are classified, they are not classified into more than three classes and Applicant suggests a three way restriction for all of the claims, assuming that Examiner can demonstrate two-way distinctness and that it would be burdensome to search all three. The argument has been considered but has not been found persuasive because classification of subject matter is merely one indication of the burdensome nature of the search involved. Although the literature searches relevant in this art would be expected to be overlapping, there is no reason to expect that they would be coextensive.Different searches and issues are involved in the examination of each group.Further, two-way distinctness has been established for the reasons set forth above. Applicants arguments have not been found persuasive and the restriction requirement is maintained.

Finally, Applicant argues that the species election (a) is improper and suggesting revising species (a) to require election of (1) tumor tissue (including cells) and extracts, (2) normal tissue (including cells) and extracts, (c) body fluids. The argument has been considered and been found persuasive and therefore all forms of tumor tissue (including cells and extracts) are hereby rejoined as one of the species of species (a), all forms of normal tissue, including cells and extracts, are hereby rejoined as one of the species of species(b) and the third species of species remains body fluids.

It is again noted that the response demonstrates that Applicant fully understands the issues in this case and that Applicant has made a full response to the restriction requirement by electing the invention to be searched. Examiner has remedied the deficiencies in the restriction requirement and has provided the necessary analysis demonstrating the two way distinctness of the inventive groups. Examiner has reduced the number of species required in the group of species (a) and

has revised the species groups to reflect the rejoinder. Examiner has rejoined Groups 141-142 to the inventions of Groups 1-96. In the interests of compact prosecution, since Applicant has elected the invention of the determination of variable 4, the likely progression of a malignant tumor in a subject, with marker (i) PAI-1 protein abundance, from Groups 1-96, has elected species A, now tumor tissue, tumor cells and extracts of thereof, has elected species B, immunoassay, has elected species C antibody secreted by clone 1, Examiner will proceed with prosecution of the elected invention together with the additional species rejoined to the tumor tissue species elected.